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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/505,191	06/24/2005	Jeffrey P. Erickson	AIB-09206	5158

7590 04/14/2008

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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
04/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,191	ERICKSON, JEFFREY P.	
	Examiner	Art Unit	
	MAGDALENE K. SGAGIAS	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15-29,32-35 and 41-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13, 15-29, 32-35, 41-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/21/08 has been entered.

Claims 1-13, 15-29, 32-35, 41-56 are pending and under consideration. Claims 14, 30-31, 36-40 are canceled.

The Declaration of Dr. Thomas Wheeler has been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13, 15-29, 32-35, 41-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a transgenic non-human mammal whose genome comprises an exogenous nucleic acid encoding at least one transgenic polypeptide, said nucleic acid operably linked to a salivary gland-specific cis-acting transcription control region of at least 4.6 Kb, wherein said polypeptide is produced in said mammal's at a level of at least 0.5 mg/ml, a

method of collecting saliva from the same transgenic non-human mammal, and a method of producing the same transgenic non-human mammal.

The specification has asserted that the invention features transgenic non-human mammals that express transgenic polypeptides in their saliva. The specification discusses that salivary gland and saliva specific regulatory elements are necessary to achieve saliva specific expression of a polypeptide of interest. See pages 26-28 of the specification. However, the guidance provided by the specification does not correlate to use of any particular saliva specific regulatory element for the creation of transgenic non-human mammals embraced by the claims. Moreover, the guidance provided by the specification is general as it does not even disclose which saliva regulatory elements could be used to create any of the transgenic non-human mammals embraced by the claims. Finally, the working examples provided by the specification (see pages 81-101) while exemplifying creation of different transgenic cows that express prothrombin and fibrinogen in their saliva respectively, did not disclose which saliva regulatory elements were used to create the transgenic cows and therefore failed to provide the skilled artisan with adequate guidance to make any of the transgenic non-human mammals embraced by the claims. Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to make and use the invention as claimed without a reasonable expectation of success.

As a first issue, the claims embrace transgenic non-human mammals that express and produce a transgenic polypeptide in saliva. The specification has discussed that saliva specific regulatory elements are necessary to achieve expression of a polypeptide of interest in saliva of a transgenic non-human mammal. See pages 26-29 of the specification. However, the guidance provided by the specification with respect to use of saliva specific regulatory elements was general and did not specifically relate to use of any particular regulatory sequence.

Moreover, the specification while suggesting that certain regulatory elements (PSP and B1-lps genes) (p 27-28) could be used failed to disclose the actual nucleotide sequences of such elements, which could direct a high level of transgene expression in saliva. This is an important point because the prior art has set forth that regulatory sequences of genes expressed in the cells of salivary gland are basically undeveloped and failed to direct high levels of polypeptide expression. See Samuelson (Annu. Rev. Phys., 1996, 58: 209-229), for example on page 217, which discussed the limitations of using the "known" promoter sequence of the parotid secretory protein (PSP) gene. Also, Samuelson provided an extensive review of the limitations of known salivary gland promoters. See throughout Samuelson. Finally, in an attempt to provide guidance as to which saliva regulatory sequence may be used within the scope of the claimed invention, the specification has relied on improper incorporation by reference of subject matter that appears to be essential. See the references to Mikkelsen, Larson and Mirels at pages 27-28 of the specification. Applicant is reminded that subject matter essential to the claimed invention may not be incorporated by reference to a non-patent publication. See 37 C.F.R. 1.57(c) and MPEP 608.01(p). In addition, the specification while is suggesting Mikkelsen and co-workers described techniques for manipulating gene expression in a transgenic animal to engender secretion of a gene product into saliva suitable for use in certain aspects of the present invention for production of desired substances in saliva of genetically engineered animals and suggest Mikkelsen et al. (1992), Nature 20(9): 2249-2255, which is incorporated herein by reference and further suggest the mouse PSP gene has been cloned and characterized by Shaw and Schibler, and by Poulsen and co-workers and suggest the region of 5' flanking DNA required for salivary gland-specific expression **is about 4.6 kb;** but, longer regions, extending farther upstream may provide higher levels of expression [0063], however, the specification has failed to provide guidance to a salivary gland-specific cis-acting

transcription control region of at least 4.6 Kb which has defined bounds of at least 4.6 Kb resulting in the production of the claimed amount of saliva in a transgenic non-human animal. **Lubon et al,** [Transfusion Medicine Reviews, X(2): 131-143, 1996 (IDS)] while reviewing the targeted expression of transgenes in transgenic animals by fusing their DNA with coding sequences to promoters of genes note many factors including cis-acting elements of gene regulatory regions, intragenic and coding sequences of heterologous genes, and the chromosomal integration site influence the tissue-specific and developmental regulation of transgenes as well as their expression (p 132, 2nd column, last paragraph). Lubon et al note in the transgenic approach, synthesis of a recombinant protein targeted to a selected cell type or organ, enabling the product to be harvested from body fluids like milk, blood, **saliva,** or urine questions with respect to transgene inheritance and stability, appropriate posttranslational modifications on heterologous proteins, industrial production procedures, and regulatory affairs have now emerged, as there are limited data published on the long-term effects of foreign protein expression on transgenic animal "bioreactor" (TAB) (abstract). Limitations will be encountered in the amount of heterologous protein expressible, as tissues synthesizing milk, blood, urine, or **saliva** need to contain some proportion of endogenous proteins for secretion and function (p 136, 1st column, 1st paragraph). Leakage may restrict the expression of certain proteins in the TAB as potential deleterious systemic effects can be envisaged for proteins of potent biological activity, such as erythropoietin, tPA, or human growth hormone (p 136, 1st column, 1st paragraph. Accordingly, given the lack of guidance provided by the specification, the skilled artisan would not know which regulatory sequence to use to achieve saliva specific expression of a polypeptide in a transgenic non-human mammal. Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the

art to make and use any of the transgenic non-human mammals embraced by the claims without a reasonable expectation of success.

As a second issue, while the claims embrace transgenic non-human mammals expressing a transgenic polypeptide in saliva, the working examples provided by specification did not provide adequate guidance that would enable one of skill in the art to create any of the transgenic non-human mammals embraced by the claims. The working examples (see pages 81-101 of the specification) discussed the creation of separate transgenic cows that expressed prothrombin and fibrinogen respectively in their saliva. However, the working examples failed to disclose which saliva regulatory elements were used in the creation the transgenic cows. As previously stated the specification as a whole has not even identified or provided the regulatory elements necessary to practice the claimed invention. A mere statement that saliva regulatory elements existed and could be used is not sufficient to enable the breadth of the claims as directed to transgenic non-human mammals expressing transgenic polypeptides in saliva. If there is no disclosure of starting material or of any conditions under which claimed process can be carried out, undue experimentation is required, and there is failure to meet enablement requirement that cannot be rectified by asserting that all disclosure related to process is within skill of art. See Genentech Inc. v. Novo Nordisk A/S 42 USPQ2d 1001, 1997. The art teaches that parotid-specific transgene expression requires an upstream cis-regulatory domain, namely the parotid control region, and this parotid control region functions with a heterologous promoter and is indispensable for achieving transgene expression and deletion of specific regions results in ectopic gene expression and the inducible expression of the transgene expression in transgenic mice decreases over 30-fold (abstract) (**Tu et al**, Gene Expr, 3(3): 289-305, 1993). In this case the starting material that has not been disclosed is the saliva regulatory element necessary to create the transgenic non-human mammals embraced by the claims. Given, the

lack of guidance and absence of working examples provided by the specification correlating to creation of transgenic non-human mammals, the lack of guidance provided by the specification with respect to use of saliva regulatory elements, the unpredictability of saliva regulatory elements, it would have required undue experimentation for the skilled artisan to practice the claimed invention.

A. Applicants argue that Samuelson only teaches PSP minigene limitations and a small parotid salivary protein promoter construct (i.e., Lama) that exhibits limited expression. Applicants argue that according to Samuelson analysis of various 5' deletion constructs of the Psp minigene localized the position of critical transcriptional control sequences for basal expression in both parotid and SLG to a region between -4.6 kb and -3.1 kb. These results indicate that the minimal salivary-specific enhancer(s) are within 5 kb of the gene and that enhancer(s) for high level expression in the parotid are located elsewhere within the 25-kb cosmid clone. Samuelson, pg 217 (emphasis added). Clearly, those skilled in the art recognized the limitation at the time and found the answer to eliminate the problem. Thus, based upon reading Samuelson, one having ordinary skill in the art would not be motivated to repeat Mikkelsen's minigene experiment using a Lama minigene and expect high level expression. Certainly, the Applicants did not. Applicants argue that the Applicants specification contemplate using promoters that are 4.6 kB or larger. See, Applicants' Specification pg 27 ln 15-16. Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the fight to prosecute the original (or similar) claims, Applicants have amended Claims 1, 20, 29, and 52 to recite that the cis-transcriptional control elements of at least 4.6 kB. This amendment is made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application.

These arguments are not persuasive because Applicants by simply contemplating that using promoters that are 4.6 kB or larger does not provide any guidance for any boundaries for designing the claimed salivary gland-specific transcription control region of at least 4.6 kB. An artisan will not be able to design specific salivary gland 5' flanking DNA required for salivary gland specific expression without set sequence boundaries. Applicants have not disclosed what are the regulatory sequences necessary to achieve saliva specific expression of a polypeptide of interest in a transgenic mammal at the claimed levels. Applicants have not correlated the use of parotid gland expression cassette, carrying all known regulatory regions in the Psp gene to the expression of a heterologous protein in the saliva of a transgenic mammal to overcome the art limitations of using the "known" promoter sequence of the parotid secretory protein (PSP) gene as discussed by Samuelson. Applicants have not disclosed the main regulatory region or enhancer in the murine PSP gene to achieve the expression of a claimed polypeptide in a transgenic mammal. Note the specification recognizes the importance of regulatory sequences, in addition to the promoter sequences such as enhancers, splice signals, transcription termination signals and polyadenylation sites, among others which are useful regulatory sequences that increase the efficiency of expression of the polypeptide and/or protein of interest in transgenic organisms." (see specification p 34).....Applicant is reminded that the subject matter essential to the claimed invention may not be incorporated by reference to a non-patent publication. The MPEP states § 1.57 Incorporation by reference:

> "Essential material" may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. "Essential material" is material that is necessary to:
> (1) Provide a written description of the claimed invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and set forth the best mode contemplated by the inventor of carrying out the invention as

required by the first paragraph of 35 U.S.C. 112;"

Note the specification points to the importance of the regulatory sequences besides the promoter for the claimed invention by emphasizing: "Among the sequences that regulate transcription that are useful in the invention, in addition to the promoter sequences discussed above, are enhancers, splice signals, transcription termination signals and polyadenylation sites, among others. Particularly useful regulatory sequences include those that increase the efficiency of expression of the polypeptide and/or protein of interest in transgenic organisms. Also particularly preferred in this regard are those that increase the specificity of expression in targeted compartments of a transgenic organism. Among highly particularly preferred regulatory regions in this regard are those that increase the efficiency, the specificity or both the efficiency and the specificity of expression in salivary glands, and the production of a desired substance thereby in the saliva of transgenic non-human animals in accordance with the invention." (see specification p 34-35). The guidance provided by the specification with respect to use of saliva specific regulatory elements was general and did not specifically relate to use of any particular regulatory sequence. Moreover, the specification while suggesting that certain regulatory elements (from PSP and B1-lps genes) could be used failed to disclose the actual nucleotide sequences of such elements, which could direct a high level of transgene expression in saliva.

B. Applicants argue use of bSP30 Promoters Do Not Require Undue Experimentation. Applicants argue the Examiner does not explain what is meant by "undue experimentation". The mere fact that some experimentation may be necessary does not allow a conclusory statement that such experimentation is undue. In fact, the Federal Circuit has supported the United States Patent & Trademark Board of Appeals by stating that: The Board observed, that "the mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been

considered to be 'undue' in this art. Indeed, great expenditures of time and effort were ordinary in the field of vaccine preparation. Falkner v. Inglis, 448 F.3d 1357, 1365 (Fed. Cir. 2006). Here, the Examiner has not shown the presence of 'undue experimentation'.

These arguments are not persuasive because at the time of filing the specification fails to correlate the endogenous expression of BSP3a and BSP30b to exogenous expression of BSP30a and BSP30b in a non-human mammal's saliva producing 0.5 mg/ml of a polypeptide in all non-human mammals as claimed in the instant application. While the Erickson declaration describes the expression of both BSP30a and BSP30b is restricted to salivary gland tissue, however the specification fails to provide guidance to an exogenous nucleic acid encoding at least one transgenic polypeptide, wherein said nucleic acid operably linked to a BSP30a or BSP30b salivary gland-specific cis-acting transcription control regions, wherein said polypeptide is produced in a non-human mammal's saliva at a level of at least 0.5 mg/ml as claimed in the instant application. The citation in the specification, p 27 that expression control regions from the gene for parotid secretory proteins ("PSP") are suitable to engineer salivary-gland specific gene expression, in the manner Mikkelsen and so-workers used control regions from the gene for mouse PSP ("moPSPW) to engender parotid-specific transgenic expression in mice, **does not** provide guidance for a BSP30a or BSP30b salivary gland-specific cis-acting transcription control regions. Moreover, the transgenic goat as disclosed in the Erickson declaration does not disclose the production of the polypeptide is produced in saliva at a level of at least 0.5 mg/ml as claimed in the instant application. As discussed in the previous office action mailed 3/26/07 pages 6-8 for example, "……..This is an important point because the prior art has set forth that regulatory sequences of genes expressed in the cells of salivary gland are basically undeveloped and failed to direct high levels of polypeptide expression. See Samuelson (Annu. Rev. Phys., 1996, 58: 209-229), for example on page 217, which discussed the limitations of

using the “known” promoter sequence of the parotid secretory protein (PSP) gene. Also, Samuelson provided an extensive review of the limitations of known salivary gland promoters. See throughout Samuelson.

C. Applicants argue incorporation by reference is not required for a known gene sequence. Applicants provide a Declaration from Dr. Thomas Wheeler that: i) the sequences of BSP30a and BSP30b were known in the art at the time of filing, and were classified as parotid secretory proteins (PSPs). See, 37 CFR § 1.132 "Declaration of Dr. T. Wheeler (hereinafter, "The Wheeler Declaration"). The Examiner is requested to note that the sequences of both the bSP30a (Tab A) and the bSP30b (Tab B) amino acid and nucleic acid sequences were made available to the public by Dr. Wheeler with a 1996 posting to GeneBank. See, The Wheeler Declaration, ¶ 2. In parallel with these sequence postings Dr. Wheeler published a 1996 paper related to bSP30 protein that not only disclosed partial amino acid sequences, but more importantly, concluded that bSP30 was not a proline-rich protein thereby suggesting that the protein more likely related to the parotid salivary proteins. Further, the 1996 Wheeler paper explicitly stated that high level bSP30 protein expression was due to genetic differences in the pSP30 promoter between the high and low bloat cattle lines. See, The Wheeler Declaration, ¶ 3. Dr. Wheeler's further work confirmed the speculation that the bSP30 protein was, indeed, a parotid secretory protein. See, The Wheeler Declaration, ¶ 4. Consequently, in 1996 (six years before the application was filed) one having skill in the art did know that the bSP30 gene was likely related to the parotid secretory protein family and the amino acid and nucleotide sequences had been published.

These arguments are not persuasive because the availability of the bovine salivary protein sequence gene and protein as accession numbers in the Gene Bank does not overcome

the lack of guidance for specific regulatory sequences that are salivary gland specific cis-acting transcription control region of at least 4.6 kB, resulting in any transgenic non-human mammal producing the claimed amount of a polypeptide in any non-human mammal.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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